ABCA1 Gene Variants Regulate Postprandial Lipid Metabolism in Healthy Men

Javier Delgado-Lista, Pablo Perez-Martinez, Francisco Perez-Jimenez, Antonio Garcia-Rios, Francisco Fuentes, Carmen Marin, Purificación Gómez-Luna, Antonio Camargo, Laurence D. Parnell, Jose Maria Ordovas, Jose Lopez-Miranda

Objective—Genetic variants of ABCA1, an ATP-binding cassette (ABC) transporter, have been linked to altered atherosclerosis progression and fasting lipid concentration, mainly high-density lipoproteins and apolipoprotein A1; however, results from different studies have been inconsistent.

Methods and Results—To further characterize the effects of ABCA1 variants in human postprandial lipid metabolism, we studied the influence of 3 single nucleotide polymorphisms (i27943 [rs2575875]; i48168 [rs4149272]; R219K [rs2230806]) in the postprandial lipemia of 88 normolipidemic young men who were given a fatty meal. For i27943 and i48168 single nucleotide polymorphisms, fasting and postprandial values of apolipoprotein A1 were higher and postprandial lipemia was much lower in homozygotes for the major alleles, total triglycerides in plasma, and large triglyceride-rich lipoprotein triglycerides. These persons also showed a higher apolipoprotein A1/apolipoprotein B ratio. Major allele homozygotes for i48168 and i27943 showed additionally higher high-density lipoproteins and lower postprandial apolipoprotein B.

Conclusion—Our work shows that major allele homozygotes for ABCA1 single nucleotide polymorphisms i27943 and i48168 have a lower postprandial response as compared to minor allele carriers. This finding may further characterize the role of ABCA1 in lipid metabolism. (Arterioscler Thromb Vasc Biol. 2010;30:1051-1057.)

Key Words: atherosclerosis • ATP-binding cassette transporters • lipids • postprandial state • triglycerides

A TP-binding cassette (ABC) transporters are a family of proteins that act as transmembrane carriers of molecules using ATP hydrolysis as the energy source.1 ABCA1, a member of the ABC family, has been implicated in monocyte differentiation and phagocyte/dendritic cell commitment,2 but the most studied aspect regarding ABCA1 is its regulation of lipid metabolism. ABCA1 is a major regulator of high-density lipoprotein (HDL) metabolism.2 Moreover, mutations in the ABCA1 gene are the underlying mechanism of Tangier disease, an affliction defined by a stark HDL deficiency, mildly to moderately increased triglyceride levels, and decreased low-density lipoprotein cholesterol.3-5 Its expression is highly influenced by intracellular cholesterol changes,9 pro-oxidant substances,10 and lipid loading (via LXR receptors).10,11 The human ABCA1 gene maps to chromosome 9q31, and its 50 exons span over 150 kbp.12,13 Although the exact physiological effects of ABCA1 are not fully understood, a role in atherosclerosis progression via reverse cholesterol pathway has been proposed.

A common strategy to indirectly define ABCA1 function has relied on assessing the clinical phenotype associated with variations in its gene. One of the most studied ABCA1 variants is R219K (rs2230806). The status of minor allele carriers has been linked to reduced atherosclerosis, with a decrease in the intima media thickness of the carotid artery,14,15 less severe coronary artery disease, and slower coronary artery disease progression.14,16 Other gene variations have also been studied, with variable effects on lipid concentrations or atherosclerosis.14,17,18 We recently reported the interaction of ABCA1 with ABCG5/ABCG8 gene variants on HDL concentration.19 However, and paradoxically, with increasing evidence for an effect of these variants on atherosclerosis and coronary artery disease comes contradiction regarding their effects on fasting lipid concentrations.14 Al-
Hospital in Cordoba, and participants previously signed an informed
committee for Clinical Investigations of the Reina Sofía University
of the participants are summarized in Table 1. The study in which
triacylglycerol concentrations
of physical activity. All volunteers had plasma cholesterol and
all subjects were encouraged to maintain regular lifestyle and levels
height, and body mass index) and blood pressure were assessed, and
they using any medication. Anthropometric measures (weight,
hour until 6 hours, and then every 2 hours and 30 minutes until 11
fat (35% saturated, 19% monounsaturated fat, 6.3% polyunsaturated
amount of fat given was 1 gram of fat and 7 mg of cholesterol per kg

though a typically plausible underlying mechanism of this altered atherosclerosis was the change in HDL concentration, this has not been found in the majority of studies.14,15
Looking for additional physiological pathways underlying ABCA1 effects on lipid metabolism and atherosclerosis, we
investigated and report here the effects of ABCA1 variants i27943, i48168, and R219K on postprandial lipid metabolism of
healthy males.

Subjects and Methods
Eighty-eight healthy men aged 18 to 33 years were selected among
students from the University of Cordoba. We included only young
normolipemic apolipoprotein E E3/E3 males to avoid possible
effects of different apolipoprotein E isoforms or gender. Other
results of this cohort have been published elsewhere.20–22 No
participants had diabetes or liver, renal, or thyroid disease, nor were
they using any medication. Anthropometric measures (weight,
height, and body mass index) and blood pressure were assessed, and
all subjects were encouraged to maintain regular lifestyle and levels
of physical activity. All volunteers had plasma cholesterol and
triacylglycerol concentrations <200 mg/dL. Baseline characteristics
of the participants are summarized in Table 1. The study in which
these participants were enrolled was approved by the Ethics Com-
mitee for Clinical Investigations of the Reina Sofia University
Hospital in Cordoba, and participants previously signed an informed
consent to join the study.

Study Design
After an overnight 12-hour fast, subjects were given a fatty meal
enriched with 60 000 U of vitamin A per m² body surface area. The
amount of fat given was 1 gram of fat and 7 mg of cholesterol per kg
body weight. This meal contained 60% of its energy in the form of
fat (35% saturated, 19% monounsaturated fat, 6.3% polyunsaturated
fat), 15% as protein, and 25% as carbohydrate, and it was consumed
within 20 minutes. After the meal, subjects were not allowed another
energy intake for 11 hours but were permitted to drink water. Blood
samples were taken just before the meal and postprandially every
hour until 6 hours, and then every 2 hours and 30 minutes until 11

hours. Taking samples at such late time points allowed many lipid
measures to return to near-fasting levels.

Biochemical Determinations
Single Nucleotide Polymorphisms Selection, DNA
Amplification, and Genotyping
R219K G>A is a well-characterized single nucleotide poly-
orphism (SNP) that has been extensively studied and is associated
with cardiovascular disease; however, its influence on postprandial
lipemia has not been tested.14 We have reported previously on other
effects of SNP i27943G>A and i48168G>A.19 Computational
analysis ascribed potential functional characteristics to each variant
allele of these SNP.19 Additionally, for the i48168 G>A poly-
morphism, analysis by MAPPER indicated a potential allele-specific
binding site for the cartilage paired-class homeoprotein 1 (CART1 or
ALXI) transcription factor, with a motif that appears enriched in
certain genes involved in cholesterol metabolism (Parnell and
Ordovas, unpublished data). Finally, both SNP showed informative
allele frequencies in reference populations. Based on these premises,
we selected these 3 SNP as good potential candidates. SNP were
genotyped using the Applied Biosystems (Foster City, Calif) Taq-
Man assay.23–25 Allele discrimination was performed on polymerase
chain reaction products. Fluorescence data were collected by a 7900
Sequence Detection System (Applied Biosystems).23

Lipoprotein Separation and Lipid Analysis
Large and small triglyceride-rich lipoproteins (TRL) were manually
extracted after centrifugation in subdued light as previously de-
scribed and samples were stored at −70°C until analyzed.25 Total
cholesterol and triglycerides (TG) in plasma and lipoprotein fractions
were assayed by enzymatic procedures.26,27 Apolipoprotein (apo) A1
and apoB were determined by turbidimetry.28 HDL cholesterol was
measured by analyzing the supernatant obtained after precipitation of
a plasma aliquot with dextran sulfate–Mg²⁺, as described.29 Low-
density lipoprotein cholesterol levels were estimated using the
Friedewald formula, based on the cholesterol, TG, and HDL chole-
sterol values.30

<table>
<thead>
<tr>
<th>ABCA1</th>
<th>R219K (rs2230806)</th>
<th>CHOL, mg/dL</th>
<th>TG, mg/dL</th>
<th>HDL, mg/dL</th>
<th>LDL, mg/dL</th>
<th>apoA1, mg/dL</th>
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CHOL indicates cholesterol; LDL, low-density lipoprotein.
P in each cell corresponds to univariate ANOVA, with each genotype as an independent factor and each phenotype variable as a
dependent factor (with age and body mass index as covariates). Within each cell, the upper genotype corresponds to homozygotes
for the major allele, the intermediate to heterozygotes, and the lower to homozygotes for the minor allele. All values are mean±SE.

*P<0.05 ABCA1 i48168 CC vs CT.
†P<0.05 ABCA1 i27943 GG vs GA.
Table 2. AUC of Lipid Fractions in the Postprandial Study

<table>
<thead>
<tr>
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<td>GG 78.5±2.8</td>
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<td></td>
<td>TT 79.9±2.7</td>
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<td>Large TRL TG</td>
<td>GG 33.4±2.5</td>
<td>CC 20.9±3.5*</td>
<td>GG 21.6±3.7‡</td>
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<td></td>
<td>TT 38.2±4.4</td>
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<td>Small TRL TG</td>
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<tr>
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<td>apoB</td>
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<tr>
<td>HDL</td>
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<td></td>
<td>TT 23.8±1.4</td>
<td>AA 23.8±1.5</td>
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Univariate ANOVA using body mass index and age as covariates. All values are expressed as (min*mg/dL)/10³. Mean±SE.

*P<0.05 ABCA1 i48168 CC vs CT and CC vs TT.
†P<0.05 ABCA1 i48168 CC vs CT.
‡P<0.05 ABCA1 i27943 GG vs GA and GG vs AA.
§P<0.05 ABCA1 i27943 GG vs GA.

Statistical Analysis

Statistical analysis methods used here are similar to those that we have published previously with respect to the gene–postprandial state interaction.20,25

Genotype Analysis

Linkage disequilibrium was tested using Helix-Tree software (Helix-Tree, version 4.3.2; Golden Helix, Bozeman, Mont.). Likelihood ratio test was used to determine the existence of linkage disequilibrium. When linkage disequilibrium was observed, r² was used to measure its strength. Using r² values, we classified linkage disequilibrium as weak (<0.30), moderate (0.30–0.80), or strong (>0.80). Hardy-Weinberg equilibrium was tested by Fisher exact test.

Analysis of Lipid Parameters

The influence of the SNP on the size of the postprandial lipid fractions was analyzed by 1-way ANOVA for area under the curve (AUC), defined as the area between the plasma concentration vs time curve, using the trapezoidal rule, with the SNP included as independent factors and body mass index and age as covariates. For any lipid fraction studied, a linear regression model was constructed to determine the influence of the covariates on the dependent variables.

Least significant difference or Games-Howell adjustments were used, depending on Levene test for homogeneity of variances. If the variances were homogeneous, then the method for correction was least significant difference adjustment, whereas nonhomogeneous variances called for applying the Games-Howell method. Repeated-measures ANOVA was also used for both the overall gene influence (global ANOVA, P for gene influence), the kinetics of the response (P for time), and the interaction of both factors (time×gene). When statistical differences were found in the repeated-measured ANOVA, a multiple comparisons test adjusted by least significant difference was applied to identify differences among the genetic isofoms on each time point of extraction. An alternative approach to the postprandial hypertriglyceridemia was performed by the accumulated TG evolution, ie, concentrations of TG were added to each previous time point to acquire each “time point accumulated TG.” For example, “time point accumulated TG” at the third hour was computed as the fasting TG concentration plus the concentrations of TG at time points 1, 2, and 3.

When minor allele homozygotes were <5% or a dominant effect of the allele was inferred, we also studied the stratified data of the mutant allele carriers vs the homozygotes for the common allele. P<0.05 was considered significant. All data presented in the text and tables are expressed as mean±SE unless otherwise specified. SPSS 17.0 for Windows (SPSS, Chicago, Ill) was used for statistical comparisons.

Results

Characteristics of participants at fasting state and genotype frequencies are shown in Table 1. The apoA1 was higher in homozygotes for the common allele of i27943 and i48168 vs heterozygotes for both SNP. HDL was higher in homozygotes for the common allele of i48168 vs heterozygotes. For the 3 SNP analyzed, there was no departure from Hardy-Weinberg (P>0.05). Pair-wise linkage disequilibrium in correlation coefficients of the 3 SNP were as follows. SNP i27943 and i48168 were in strong linkage disequilibrium (P<0.05; r²=0.827), R219K was not in linkage disequilibrium with either of the other 2 SNP (r²<0.012; P>0.05). The influence of the SNP on postprandial lipid levels is described and is summarized in Table 2 and Figures 1–3.

R219K

A statistical study is presented for a genotype-dominant effect based on previously published data.14 In parallel, an additive model was also performed but we did not observe any differences compared with the dominant model. A trend for lower fasting TG and large TRL TG was found in minor allele carriers compared to major allele homozygotes (P=0.056 and P=0.070, respectively; Table 2). We did not find other significant differences in the postprandial lipid metabolism.

i48168

Individuals with the CC genotype for i48168 (homozygotes for the common allele) showed a lower AUC for total TG compared to the other 2 genotypes (P=0.006 vs TT and P=0.025 vs CT; Table 2). In the repeated-measures ANOVA, we found lower TG for CC vs TT from hours 1 to 8.5, and vs CT from time points 2 to 5 (Figure 1A). CC participants had lower AUC of large TRL TG than the other 2 groups (Table 2). The differences were noted at time points 3 to 8.5 vs TT, and 2 to 6 vs CT (Figure 1B).

Subjects homozygous for the major allele displayed lower amounts of accumulated TG from the third hour to the end of
the study compared to CT and TT (all \( P < 0.05 \); Figure 2A). We found no differences in the postprandial state for total cholesterol, large TRL cholesterol, small TRL cholesterol, or small TRL TG, depending on this SNP. A trend for higher AUC of HDL was noted for CC homozygotes vs heterozygotes (\( P = 0.074 \)). In the repeated-measures ANOVA, the differences were significant at fasting in CC vs CT (\( P = 0.006 \)). AUC of apoA1 was higher in CC subjects than in CT subjects (\( P = 0.006 \)). The apoA1/apoB ratio was higher in CC vs TC individuals (\( P = 0.008 \)).

**Discussion**

Persons homozygous for the major alleles of ABCA1 SNP i27943 and i48168 have lower postprandial lipemia than carriers of minor alleles (in healthy young men). These results derive from a highly controlled, standardized trial of apoE E3/E3 participants who were subjected to a lipemia test meal. The interaction between genes and postprandial lipemia is well-reported.31 The complexity of conducting a study with hourly blood draws and a total duration of 11 hours is high; therefore, this type of study is rarely conducted and cannot be performed in larger and broader epidemiological studies because of methodological issues. Although other simpler designs for postprandial lipemia assessment have been reported, our method allows deep evaluation into the postprandial state.32

The relationship between ABCA1 polymorphisms and altered atherosclerosis is well-stated.14,17,33 To date, the strongest associations have linked ABCA1 variants with altered HDL concentrations,14,18,34 which are probably mediated by apoA1 metabolism.15 However, these variations in HDL have not been stated universally. Furthermore, in a recent report of type 2 diabetic patients, the ABCA1 SNP associated with coronary heart disease (including R219K) were not associ-
ated with HDL, and those associated with HDL were not associated with coronary heart disease.\textsuperscript{35} The explanation for these contradictory findings has been set on the limited effects that gene variation can have on final HDL levels, gene–environment interactions, or the influence of \textit{ABCA1} gene variants on other lipid molecules and enzymes that secondarily can mildly influence HDL concentrations.\textsuperscript{17}

The minor allele of R219K has been associated with limited atherosclerosis,\textsuperscript{15} reduced risk for myocardial infarction, or progression of coronary disease in various studies.\textsuperscript{16,36–42} Here, we noticed only a trend toward lower fasting TG (\(P=0.059\)), according to previous studies.\textsuperscript{14} Currently, this variant is thought to affect lipids mildly, but gene–environment interactions are strong, with greater effects on lipid concentration when oxidative stress or inflammation is elevated in subjects.\textsuperscript{14,15,39,40} Such is not the case in our study. However, marginal effects not reaching significance were found in our study for practically all lipid parameters toward a protective effect for the minor allele of R219K, which could become significant when the subject is exposed to the aforementioned stressors or even simply with increasing age.

Because SNP i27943 and i48168 are in strong linkage disequilibrium in our population, it is possible that part of the results obtained for 1 SNP may be attributable to linkage disequilibrium and not to real functional effects. If this were the case, then we hypothesize that i48168 has a greater likelihood to be the functional SNP based on 3 points. First, i48168 has been shown to influence lipids in which i27943 showed no effects.\textsuperscript{19} Second, computational analysis indicated a potential allele-specific binding site for the cartilage paired-class homeoprotein 1 (CART1) transcription factor, whose motif appears enriched in certain genes involved in cholesterol metabolism.\textsuperscript{19} Third, the significance coefficient (\(P\)) was lower when the 2 SNP were observed to influence the same lipid parameters. Although part of the effects may be secondary to their high linkage disequilibrium, other findings support that both variants have differential effects. In this sense, i27943 alone showed association to altered plasma apoB levels in the postprandial state.

Our results show that homozygotes for the common alleles of i27943 and i48168 had lower postprandial increases in TG and large TRL TG, indicating a lower lipemic response and lower fasting and postprandial apoA1 levels. The effects on TG (TG and large TRL TG) were observed with an “additive model” in the sense that heterozygotes were more similar to homozygotes for the major allele, and minor allele homozygotes showed the highest postprandial lipemia. Furthermore, the accumulated TG in the postprandial state showed time-dependent divergent lines for each genotype, which manifests as an accumulation of TG (clearance delay) during the postprandial period. In HDL, we only noted a higher fasting value for i48168 common allele homozygotes vs heterozygotes. Major allele homozygotes for i27943 showed lower apoB concentrations in the postprandial state but, curiously, not in the fasting state. In both cases, homozygotes for the major alleles displayed a higher apoA1/apoB ratio than heterozygotes, which has been associated with cardiovascular risk.\textsuperscript{43}

There is a lack of studies describing effects of these 2 SNP on human lipid metabolism. A recent study from our group in a cohort of Puerto Rican participants (aged 45–70 years), living in Boston, Massachusetts, reported an interaction of i48168 with \textit{ABCG5} and \textit{ABCG8} variants to determine HDL levels.\textsuperscript{19} \textit{ABCG5}/\textit{ABCG8} SNP were associated with differences in HDL concentration only in minor allele homozygotes. The lower HDL in carriers of the minor allele found in our study can support the theory that these persons have some deregulation of HDL metabolism that leads to different HDL values, just as we observed, or leads to a higher susceptibility of altered HDL concentration when exposed to other gene variants, as in the study in Puerto Rico.

To the best of our knowledge, this is the first report of postprandial data on these 2 \textit{ABCA1} SNP, probably because HDL metabolism has been the primary focus of research in humans. Nevertheless, animal models have repeatedly shown effects on the postprandial state, although the influence of loss of \textit{ABCA1} function has been linked to increased and decreased postprandial triglycerides.\textsuperscript{34,43} Furthermore, and supporting postprandial effects of these proteins in humans, patients with Tangier disease follow a pattern similar to the one that we observed, with delayed TG clearance.\textsuperscript{46} In a recent review of metabolic regulation of intestinally derived lipids, these apparent contradictory findings were noted, with the authors stating, “clearly, either positively or negatively, \textit{ABCA1} appears to influence postprandial lipid metabolism.”\textsuperscript{36}

Further study is clearly required to unify the classic model in which effects of \textit{ABCA1} polymorphisms were found mainly in apoA1 and HDL concentrations with our results, in which most of the effects appear to be produced in the postprandial state. This is probably best accomplished by in vitro/in vivo studies, which will require a focus on the
postprandial clearance of particles in models with these SNP. In our opinion, apoA1 may be the cornerstone of the effects found with SNP i48168 and i27943. As is broadly known, apoA1 protein is mainly present in HDL cholesterol. However, it is also present on the surface of nascent chylomicrons. We have reported recently that an apoA1 SNP (apoA1 −2803; [rs277784]) clearly influences postprandial lipemia in healthy males.26 Furthermore, effects of this variant on postprandial lipemia were quite similar to those we report here that show a clear influence on the molecules that initiate postprandial metabolism, such as total and large TRL TG (which express apoA1 on their surface), and that show no effect on molecules implicated in the final phase of postprandial metabolism (mainly small TRL), which do not express apoA1 in their surface. Our explanation for the effects of apoA1 −2803 variant, which also can be applied on the ABCA1 SNP reported here, stated that effects of the variant on postprandial metabolism may be mediated by altered levels of apoA1 present on the surface of large TRL. Supporting this theory, we have found alterations in total apoA1 concentrations depending on the ABCA1 variants i48168 and i27943.

In conclusion, in our study, healthy young men carrying the minor alleles for i48168 and i27943 of ABCA1 show much higher postprandial lipemia. This feature has been associated with a higher risk for accelerated progression of atherosclerosis and eventually cardiovascular disease, but identification of phenotype association in a clinical trial to increase cardiovascular risk can be overlapping and requires further investigation. Extrapolation to other age groups or to people with associated conditions, however, may not be correct, because it has been reported that the effects of other variants of ABCA1 on lipid metabolism are highly dependent on those factors.

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Disclosures
None.

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